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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/196,154	11/16/1995	PHILIP O. LIVINGSTON	43016-A-PCT-	5954

7590 06/10/2003

JOHN P WHITE
COOPER AND DUNHAM
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1642	37

DATE MAILED: 06/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/196,154	LIVINGSTON ET AL.	
	Examin r	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The amendment filed March 31, 2003 is acknowledged. Claims 97, 101-111 and 113-118 were canceled. Claims 119-143 were added.

2. Claims 119-143 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The provisional rejection of claims 119-143 as under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending application No 08/475,084 is withdrawn because the claims of the instant application are drawn to conjugates comprising a GM2 ganglioside whereas the claims of 08/475,084 are drawn to conjugates comprising a GD3 ganglioside.

5. The provisional rejection of claims 119-143 as under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending application No 08/477,147 is withdrawn because the claims of the instant application are drawn to conjugates

comprising a GM2 ganglioside, whereas the claims of 08/477,147 are drawn to conjugates comprising a GD2, GD3 lactone, O-acetyl GD3 or GT3 ganglioside.

Rejections Maintained:

6. The prior objection to the disclosure is maintained for the reasons as set forth in the Office Action mailed 6/19/98 (see Paper No. 16).

Applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. Until applicants submit a proper Figure said objection is maintained.

7. The provisional rejection of claims 119-143 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 101-126 of copending Application No. 08/477,097 is maintained for reasons of record, as applicant argues only that the rejection should be withdrawn if the claims are found allowable.

8. Claims 119-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989) in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

Wiegand discloses modified glycosphingolipids (GM3, GD3, GM2 and GM1). Wiegand discloses a method for chemical modification of the sphingoid portions of glycosphingolipids to make glycosphingolipids capable of coupling to proteins (see abstact). Wiegand discloses that the method of chemical modification is that of ozonolysis at the C-4 double-bond of the sphingosine base resulting in the formation of a reactive aldehyde species (col. 2, line 43 - col. 3, line 67). Wiegand discloses that the aldehyde group is susceptible to reductive amination. Wiegand fails to disclose conjugation of the modified glycosphingolipid to KLH via an amine linkage between the C-4 carbon of sphingosine base and an ε-aminolysyl group of KLH. Wiegand also fails to disclose a composition that comprising a saponin derivable from the bark of the Quillaja saponaria Molina Tree (QS-21).

Fiume (1988) teaches that reductive amination of reactive aldhehyde species with proteins having ε-lysine groups is well known in the art (see page 268-269). Specifically, Fiume teaches that aldehyde group of a galactosyl residue may be reacted with an ε-lysine of a protein.

Ritter (1991) teaches that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (page 406, paragraph 1). Ritter teaches that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al also teach that

the immune responses obtained with QS-21, reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

Maricani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the modified GM2 glycosphingolipids of Wiegand to make a GM2 glycoconjugates that are the same as those claimed. Weigand teaches a modified glycosphingolipid that has a reactive aldehyde group (at the C-4 position of the sphingosine base) that may be used for coupling to proteins as taught by Fiume, because Fiume demonstrates that methods of reductive amination to link proteins, via ε-lysine residues, to reactive aldehyde groups is known in the art. Because Wiegand teaches a method of ozonlysis that results in the formation of a reactive aldehyde species, the bond that would be formed between the C-4 carbon of the sphingosine base and the KLH would be an amino linkage that would cause the C-4 carbon to be present in a CH_2 group. It would have been further prima facie obvious to one of ordinary skill in the art to have used KLH as the protein carrier because, as Ritter teaches, attachement of gangliosides to carrier proteins such as KLH increase IgG responses to gangliosides. It would have been prima facie obvious to one of ordinary skill in the art to add QS-21, because, as taught by Kensil, it provides for a higher antibody response, and QS-21 provides the advantages that it is not toxic to animals (see Marciani).

It also would have been prima facie obvious to optimize the doses of QS-21 in the composition, also it would have been prima facie obvious to one of ordinary skill in the art to optimize the weight ratio of the components of the composition to provide an optimal response.

One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the e-aminolysyl groups of carrier proteins for enhance immunogenicitiy is routine in the art and, as Uemura (1976) teaches, ozonolysis and reduction of various sphingolipids does not affect the haptenic reactivity with antibodies.

9. Claims 119, 129-132 and 134-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989), Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988) Livingston et al. (Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976).

As discussed above, Wiegand in combination with Fiume teaches a glycoconjgate as claimed in claims 119 or 129.

Livingston teaches that melanoma recurrence was delayed in patients developing GM2 antibodies after treatment with the composition (page 7048, paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (pate 7047, paragraph bridging columns 1-2). Livingston et al also teach

the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2).

Ritter (1991) teaches that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (page 406, paragraph 1). Ritter teaches discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

Livingston et al (U.S. Patent No. 5, 102,663) teach that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28).

Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al also teach that the immune responses obtained with QS-21, reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

Maricani et al teach the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the modified GM2 glycosphingolipids of Wiegand to make GM2 glycoconjugates that are the same as those claimed, and then to have used the glycoconjugates in compositions for the stimulating or enhancing antibody production or in a method of treating cancer, because Livingston teaches that melanoma recurrence is delayed in patients developing GM2 antibodies after treatment with vaccines comprising GM2 (page 7048, paragraph 1 and column 2, paragraph 2). Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (page 7047, paragraph bridging columns 1-2). Livingston et al also teach the ganglioside GM2 is expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have added QS-21 as an adjuvant to the GM-2-KLH conjugate for use as a vaccine because the conjugated composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al (1991), thus providing the advantages by Ritter et al (1991) and, as Kensil teaches, adding the QS-21 is advantageous because it provides for a higher antibody response that the commonly used adjuvant . Also, QS-21 provides the advantages that it is not toxic to animals (see Marciani).

It also would have been prima facie obvious to optimize the doses of QS-21 in the composition, also it would have been prima facie obvious to one of ordinary skill in the art to optimize the weight ratio of the components of the composition to provide an optimal response.

One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the e-aminolysyl groups of carrier proteins for enhance

immunogenicitiy is routine in the art and, as Uemura (1976) teaches, ozonolysis and reduction of various sphingolipids does not affect the haptenic reactivity with antibodies.

Optimization of the dosage, route of immunization, number of sites of immunization to administer the composition is will within the skill of the ordinary artisan.

One would have reasonably expected the conjugation procedure to work as substituted because conjugation through the e-aminolysyl groups of carrier proteins for enhance immunogenicitiy is routine in the art and Uemura et al (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies.

10. The rejection of claim 132 and 133 under 35 U.S.C. 103(a) as being unpatentable over Wiegand et al (U.S. Patent 5,599,914; issued Feb. 4, 1997; filed Nov. 24, 1989), in view of Fiume et al (Critical Rev. Therapeutic Drug Carrier Systems, 4(4): 265-284, 1988) Livingston et al. (Cancer Research, 149:7045-7050, 1989), Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al.(The Journal of Immunology, 146(2):431-437, 1991), Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al (J Biochem, 79(6):1253-1261, 1976) as applied to claims 78, 80-92, 94 and 96-99 above and further in view of Irie et al. (U.S. Patent Nol 4,557,931).

The teachings of Wiegand , Fiume, Livingston et al.(1989), Ritter et al. (1991), Livingston et al. (U.S. Patent No. 5,102,663), Kensil (1991), Marciani (1991) and Uemura (1976) are discussed above. The combination differs by not teaching the administration of the composition for treating cancer of epithelial origin.

Irie et al teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer the GM-2-KLH conjugate/ QS-21 composition or other ganglioside conjugate/QS-21 composition as combined supra to patients afflicted with or susceptible to a recurrence of cancer of an epithelial origin (i.e. breast carcinomas) because the ganglioside GM-2 is found in the stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the composition react with the tumor and treat the disease.

Response to Applicant's Arguments:

11. Applicant argues that the claimed inventions are not obvious over the prior art, because Weigand teaches how to make glycoconjugates generally and does not disclose any species of glycoconjugate that is any better than any other. This argument is not persuasive, because the standard for obviousness is that the prior art as whole is compared to the claimed inventions. Thus, arguing a deficiency in Weigand is insufficient to overcome the present grounds of rejection. Furthermore, Weigand does disclose specific species of glycoconjugates, (GM3, GD3, GM2 and GM1), which may be made by the disclosed method. Additionally, the prior art as whole teaches specific glycosides that are useful as tumor antigens and provides motivation to make specific species.

New Grounds of Rejection:

12. Claims 122-124 and 143 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the addition of these claims introduces new matter into the specification as originally filed.

Claims 122-124 recite ranges that are not described in the specification. Claim 143 is drawn to a method for delaying recurrence of melanoma. There does not appear to be support in the specification for methods for delaying recurrence of melanoma. The passages pointed to by applicant as providing support do not teach the recited references and do not teach methods for delaying the recurrence of melanoma.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
June 4, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600